Case report

A Case of Irinotecan-Induced Pneumonitis

Ken-ichiro Inoue, Noriya Hiraoka, Yoshihiro Kasamatsu,
Yutaka Kawahito, Keiji Yoshioka, and Sadayoshi Yokoo

Abstract: We report a case of pneumonitis caused by irinotecan (CPT-11). A 55-year-old man was admitted for further evaluation and treatment of small cell lung cancer (SCLC). After irradiation for a focal brain metastatic lesion, irinotecan was administered intravenously. Three weeks after the chemotherapy, he had a high fever with diffuse patchy attenuation on a chest computed tomography (CT) scan. A significant increase in the number of mast cells in his bronchoalveolar lavage (BAL) fluid was also found. The pneumonitis was subsequently controlled by steroid therapy, with a decrease in the number of mast cells in the BAL fluid.

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Key words: Irinotecan, Small cell lung cancer, Pneumonitis, Bronchoalveolar lavage, Mast cell

1. Introduction

The new camptothecin derivative irinotecan([CPT-11], 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyl-oxycamptothecin), is a topoisomerase I inhibitor and has been proven to have positive effects against lung cancer[1),2)]. The adverse effects of irinotecan are bone marrow suppression and refractory diarrhea. A few cases of pulmonary disease have also been previously reported, as a reverse reaction to irinotecan. Moreover, there have been no reports on bronchoalveolar lavage (BAL) fluid findings of pulmonary disease caused by irinotecan. We describe herein a patient with small cell lung cancer (SCLC) who developed pneumonitis after treatment with irinotecan, in which a significantly increased number of BAL mast cells were observed.

2. Case report

A 55-year-old man was referred to our hospital in February 1998 for further treatment of SCLC. The patient had been diagnosed with SCLC located in S^{10} plus bone metastases in 1993, and have received 20 courses of combination chemotherapy. He had experienced no adverse effects due to chemotherapy. Chemotherapy consisted of etoposide, carboplatin, and vincristine sulfate. In January 1998, he was admitted to our hospital because of brain metastases.

Results of a physical examination on admission were a normal result except for decreased respiratory sounds in the lower region of the left lung field. The laboratory data were as follows: hemoglobin concentration, 10.7 g/dl; leukocyte count, 5100/μL with 74% neutrophils, 0.7% basophils, and 1.3% eosinophils. The erythrocyte sedimentation rate (ESR) was 40 mm/hr, and the LDH level was 187 IU/L. His neuron specific enolase (NSE) and pro gastrinreleasing peptide (GRP) levels were elevated to 30 ng/mL and 648 pg/mL, respectively. Arterial blood gas analysis with room air showed a PaO_2 of 96 mmHg, a $PaCO_2$ of 36 mmHg, and a pH of 7.45. The other laboratory findings, including renal and hepatic profiles and urinalysis, were normal. A chest X-ray film showed mass opacities in the lower left field.

At first, the patient underwent focal irradiation to the metastatic brain lesion (gamma knife), and the size of the tumor decreased. Thereafter, weekly systemic chemotherapy consisting of 65 mg/m^2 of irinotecan was initiated in March 1998. He received no other drugs except for 3 mg of granisetron intravenously before the administration of the anticancer drugs. Three weeks after the initiation of his chemotherapy (total dosage of irinotecan 180 mg/m^2), he developed a high fever (38.0℃), but had no other complaints such as a cough or dyspnea. The laboratory data at that time were as follows: leukocyte count, 2000/μL, with 53% neutrophils, 0.6% basophils; and 4.7% eosinophils. The ESR was 40 mm/hr, and the LDH level was 128 IU/L. A chest X-ray film disclosed no specific findings except for mass shadows in the lower left field (Fig. 1). His fever did not improve despite antibiotic therapy for suspected bacterial infection. Arterial blood gas analysis with room air showed a PaO_2 of 105 mmHg, a $PaCO_2$ of 34 mmHg and a pH of 7.42. A chest CT scan revealed a diffuse distribution of patchy areas with a ground-glass appearance (Fig. 2). A fiber-optic bronchoscopy was then performed. In a BAL fluid sample, the total cell count was 3.6×10^5/ml in-

First Department of Internal Medicine, Matsushita Memorial Hospital, Osaka, Japan.

Fig. 1. A chest X-ray showing mass opacities in the left lower lung field (March 6, 1998).

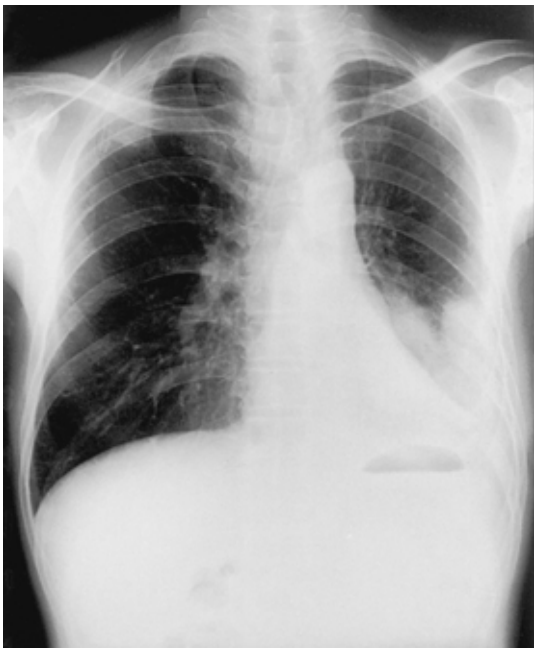
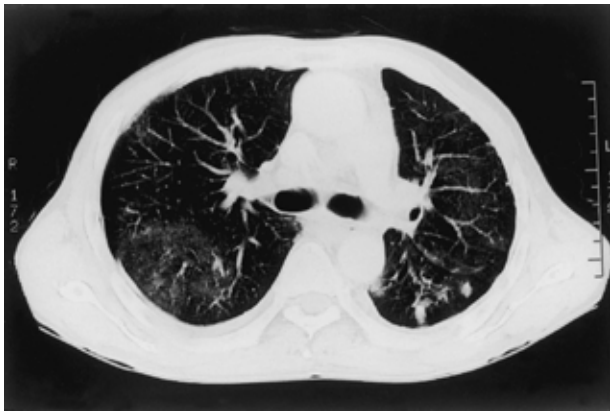


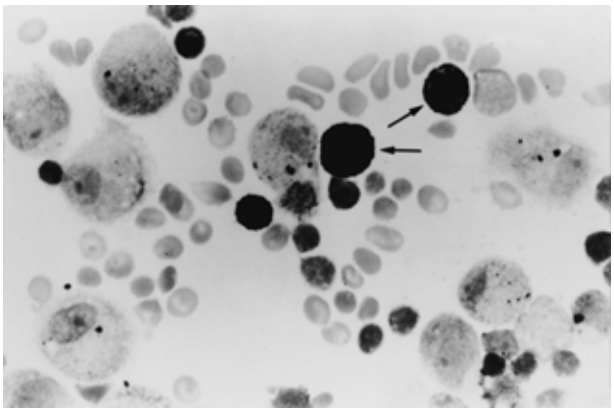
Fig. 2. A chest CT scan revealing patchy areas with a ground-glass appearance (March 8, 1998).



cluding 25% lymphocytes, 2% eosinophils, 71% macrophages, 1.0% neutrophils, and 1.0% mast cells (Fig. 3). The CD4+/CD8+ ratio was 1.56, and a BAL fluid culture contained no bacteria, fungi, pneumocistis carinii, or acid-fast organisms. A transbronchial lung biopsy was not performed because of his bleeding tendency.

Under a diagnosis of interstitial pneumonia due to irinotecan, the chemotherapeutic medication was discontinued. Methylprednisolone sodium succinate was then administered intravenously (250 mg/day for 3 days), followed by an oral administration of prednisolone (40 mg/day). The patient responded well and became afebrile. A

Fig. 3. BAL fluid sample showing an increased number of mast cells (March 9, 1999).



chest CT scan revealed the disappearance of the diffuse, pachy shadows one week later. One month after the initiation of the corticosteroid therapy, a second BAL was performed ; the dosage of prednisolone was 20 mg/day at that time. The total cells were 0.4×10^5/ml, including 7% lymphocytes, 1% eosinophils 90.5% macrophages, 1.2% neutrophils, and 0.1% mast cells. He then received radiotherapy for the lung cancer (total of 48 gray), which decreased the size of the tumor. The steroid dosage was subsequently tapered off and stopped, and the patient was discharged from the hospital 4 months after admission.

3. Discussion

It is well known that myelosuppression and diarrhea are the major adverse reactions of irinotecan[1),2)]. With respect to pulmonary toxicity due to irinotecan administration, Oshita et al.[2)] reported that interstitial pneumonia appeared in 3 of 61 patients (4%) who received combination chemotherapy of irinotecan and etoposide. In their report, the patients were diagnosed with interstitial pneumonia over 3 courses of chemotherapy, and showed hypoxemia with a diffuse reticular shadow on chest X-ray films. Masuda et al.[1)] reported that they have to experience of observing two patients (13%) with pulmonary toxicity after the administration of five and seven doses of irinotecan (dosage of 100 mg/m^2). The chest X-ray films of these two patients showed a diffuse reticulonodular pattern.

The present case showed the presence of chest radiographic abnormalities in addition to a high fever after three weeks of irinotecan administration. The patient did not receive any other medications besides irinotecan and granisetron. Therefore, the irinotecan was the most prob-

able cause of the pneumonitis in this patient. However, our patient is quite different from those discussed in the previous reports because he did not have hypoxemia and his CT scan revealed a ground-glass pattern.

The BAL fluid findings of our case were consistent with drug-induced interstitial pneumonia, i. e., a general increase in both total cell counts and lymphocytes without a high CD4＋/CD8+ ratio. It has been suggested that T lymphocyte suppressor cells may play an important role in regulating fibrosis of drug-induced pulmonary diseases[3]. To our knowledge, this is the first case report describing the BAL fluid finding of a pulmonary disease caused by irinotecan. The present case is also of interest in that an increased number of mast cells were apparent in the BAL fluid. Although the dosage of the corticosteroid used against the pulmonary disease caused by irinotecan was clearly not standardized, our patient experienced both clinical and radiological improvements with intermediate doses of a corticosteroid. The second BAL performed after the corticosteroid therapy revealed a decrease in the mast cells. With regard to the pathological mechanisms in which mast cells play a role in patients with pulmonary diseases, Haslam and colleagues[4] indicated that chemical mediators such as histamine released from the mast cells could increase the permeability of pulmonary vessels. This would, in turn, allow the increased access of inflammatory cells into the interstitial tissues, thus aiding the development of the granulomatous lesions. Askenase and Van Loveren[5] proposed that the initiation of a delayed hypersensitivity response depended on the release of vasoactive mediators from mast cells activated by antigen-specific T-cell-derived factors. On the other hand, Pesci et al.[6] showed significant increases in the number of mast cells and tryptase levels in BAL fluid of patients with idiopathic bronchiolitis obliterans organizing pneumonia（BOOP）, thus suggesting that mast cells play a primary role in fibrosis. However, there have been no previous reports or investigations describing mast cells in the BAL fluid of patients with drug-induced pulmonary diseases. The increased number of BAL mast cells in the present case suggests that mast cells may contribute to drug-induced pulmonary diseases by irinotecan.

In conclusion, clinicians should be alert to the possible occurrence of pulmonary disease when irinotecan is used. In addition, mast cells may play an important role in the pathogenesis of pulmonary diseases due to irinotecan.

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